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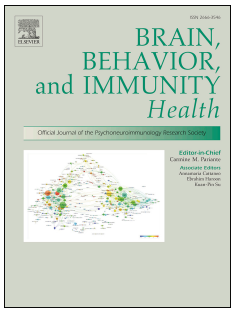


# Association of serum interleukin-6 and C-reactive protein with depressive and adjustment disorders in COVID-19 inpatients

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PII: S2666-3546(21)00208-8

DOI: https://doi.org/10.1016/j.bbih.2021.100405

Reference: BBIH 100405

To appear in: *Brain, Behavior, & Immunity - Health*

Received Date: 9 December 2021

Accepted Date: 10 December 2021

Please cite this article as: Iglesias-González, M., Boigues, M., Sanagustin, D., Giralt-López, M., Cuevas-Esteban, J., Martínez-Cáceres, E., Díez-Quevedo, C., Association of serum interleukin-6 and C-reactive protein with depressive and adjustment disorders in COVID-19 inpatients, *Brain, Behavior, & Immunity - Health* (2022), doi: https://doi.org/10.1016/j.bbih.2021.100405.

**TITLE**: Association of serum interleukin-6 and C-reactive protein with depressive and adjustment disorders in COVID-19 inpatients.

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***Word Count:*** 3,817

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## ABSTRACT

**Background**: Immune mechanisms are part of the pathophysiology of mental disorders, although their role remains controversial. In depressive disorders a chronic low-grade inflammatory process is observed, with higher interleukin-6 (IL-6) values. Furthermore, in SARS-CoV2 infection, which is closely related to depressive disorders, there is a proinflammatory cascade of cytokines that causes systemic inflammation.

**Methods**: The present study evaluates the relationship between IL-6 and C-reactive protein (CRP) serum levels and the presence of depressive and adjustment disorders in a sample of 1851 patients admitted to hospital for SARS-CoV2 infection from March to November 2020. Concentrations of IL-6 and CRP were determined within the first 72 hours at admission and compared among groups of patients according to previous history and current presence of depression or adjustment disorders.

**Results**: IL-6 serum levels were significantly higher in the group of patients with depression and adjustment disorders compared to patients without such disorders (114.25 pg/mL (SD, 225.44) vs. 86.41 (SD, 202.97)), even after adjusting for several confounders. Similar results were obtained for CRP (103.94 mg/L (SD, 91.16) vs. 90.14 (SD, 85.73)). The absolute levels of IL-6 and CRP were higher than those of previous depression studies, and differences were only found for the subgroup of *De Novo* depressive or adjustment disorders.

**Conclusions**: Serum concentrations of IL-6 and CRP are higher in COVID-19 patients with *De Novo* but not persistent depressive or adjustment disorders. Clinical features such as fatigue, asthenia, anhedonia, or anxiety can be the basis for this finding.


**Keywords:** Inflammation, immunity, depression, anxiety, COVID-19, cytokines

## 1. INTRODUCTION

Depressive disorders are a common mental illness and one of the most important causes of disability (Lim et al., 2018). Nevertheless, the pathophysiology of depression is still controversial. In addition to changes in neurotransmission, neurotrophy, or neurotoxicity, immune mechanisms have received a great deal of attention in recent years. Several lines of evidence have been involved in the association between immune processes and depressive disorders: 1) cross-sectional studies have found higher concentrations of pro-inflammatory cytokines in peripheral blood of patients with depressive disorders, mainly C-reactive protein (CRP), interleukin 6 (IL-6), interleukin 12 (IL-12) and tumor necrosis factor-α (TNFα) (Köhler et al., 2017; Ting et al., 2020); 2) exogenous administration of pro-inflammatory cytokines (for instance, interferon-α) usually induce clinical depression in medical patient (Martín-Santos et al., 2008; Musselman et al., 2001; Schaefer et al., 2012); 3) there is considerable overlap between depressive symptoms and those of the inflammatory response, which behavioral repertoire is often referred to as "sickness behavior" (Capuron and Castanon, 2017; Miller and Raison, 2016); 4) infections and autoimmune diseases in childhood are associated with an increased risk of depression in adults (Benros et al., 2013); or 5) clinical trials demonstrating the antidepressant power of some anti-inflammatory drugs (Kappelmann et al., 2018).

However, the specific role that inflammatory processes play in the pathophysiology of depression is still debated (Debnath et al., 2021). It may be that the association is only present in a subset of depressed patients representing a differentiated phenotype (Khandaker et al., 2017), or with some specific dimensions of symptoms beyond categorical diagnoses, such as fatigue, anxiety, or arousal (Capuron and Castanon, 2017). Similarly, it is increasingly evident that inflammatory markers are not only

elevated in depressed patients, but also in patients with other neuropsychiatric disorders (Goldsmith et al., 2016; Pinto et al., 2017), including anxiety disorders (Michopoulos et al., 2015; Renna et al., 2018). Furthermore, evidence from animal as well as clinical studies seems to indicate that increased peripheral or central IL-6 levels play an important role in stress reactions (Ting et al., 2020).

Specifically, IL-6 exhibits two contrasting features (Gabay, 2006): In models of acute inflammation, IL-6 shows an anti-inflammatory profile by removing infectious agents and repairing tissues through activation of immune and acute-phase responses (Xing et al., 1998). When such stress has been eliminated from the host and homeostasis is fully recovered, IL-6 synthesis is terminated. In contrast, in models of chronic diseases, IL-6 not only serves as an inducer of acute phase reactions but acts also as a proinflammatory agent (Alonzi et al., 1998; Yamamoto et al., 2000) by eliciting cellular immune responses to affected cells and mucosal humoral responses. In these cases, IL-6 has a detrimental role that favors mononuclear cell accumulation at the site of injury that may persistently increase serum levels of IL-6 and provide the basis for the amplification step of chronic inflammatory proliferation (Atreya et al., 2000).

Previous evidence has shown a relation between chronic immune-mediated inflammatory diseases, such as rheumatoid arthritis (Nerurkar et al., 2019) or inflammatory bowel disease (Neuendorf et al., 2016) and depressive symptoms, and, although less studied, anxiety and affective symptoms have also been reported in acute infections, such us acute HIV infection (Hellmuth et al., 2017).

Meanwhile, severe forms of COVID-19 seem to mainly develop because SARS-CoV2 infection induces an inflammatory cascade that releases pro-inflammatory cytokines such as IL-6, IL-1β, IL-18, and IL-33 (Chen et al., 2019; Kritas et al., 2020). These cytokines involve physiological responses that lead to systemic inflammation and the

alterations observed in COVID-19, such as neutrophilia, lymphopenia and the up-regulation of CRP and other acute phase reactants (Yormaz et al., 2020). The high production of IL-6, together with the Macrophage Activation Syndrome contributing to lung inflammation in COVID-19 disease, may explain the high serum levels of CRP, which are normally lacking in viral infections (McGonagle et al., 2020). Patients with severe forms of COVID-19 disease present a cytokine storm that correlates with immune exhaustion and poor therapeutic outcome (Huang et al., 2020; Liu et al., 2021).

There is also growing evidence of the high prevalence of mental disorders in patients suffering from COVID-19, especially mood and anxiety disorders (Diez-Quevedo et al., 2021; Vai et al., 2021). Previous studies have evaluated the relationship between psychological distress and inflammatory biomarkers. However, systemic inflammation does also compromise the blood-brain barrier and floods the brain with pro-inflammatory factors. Thus, the virus may also infect the brain triggering reactive gliosis and leading to an increased production and secretion of cytokines and other pro-inflammatory factors. Systemic inflammation, hypoxia and neuroinflammation may trigger or exacerbate psychiatric diseases (Steardo et al., 2020). A mixed-method study revealed that depression levels were statistically directly related to the levels of CRP among patients with depressive symptoms, with the more improvement of CRP levels from baseline, the lower scores of depressive symptoms (Guo et al., 2020).

Therefore, the objective of this study is to evaluate the association of IL-6 and CRP in COVID-19 patients and their correlation with the presence or onset of depressive or extended adjustment disorders.

## 2. METHODS AND MATERIALS

### 2.1. Subjects

All adult patients with a positive result for the SARS-CoV-2 polymerase chain reaction (PCR) who were admitted to a tertiary university hospital in Badalona (Spain) throughout the period between March 1 and November 17, 2020, were included in the study. All patients suffered from severe forms of SARS-COV2 infection that had to be cared for in a tertiary hospital setting. All procedures contributing to this work complied with the ethical standards of the national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures were approved by the Research Ethics Committee from Germans Trias i Pujol University Hospital (reference number: AC-20-031-HGT-CEIM). Informed consent was not collected as this was a retrospective study and all data were extracted anonymously from computerized records.

### 2.2. Data collection

The hospital's Department of Information Systems anonymously extracted patients' computerized clinical data from several hospital-based and primary care-based platforms. Data included sex and age, previous year medical and psychiatric disorders, medical complications during admission, and results of blood tests carried out. Psychiatric diagnoses were made according to the diagnostic criteria of the International Classification of Diseases, 10th edition (ICD-10), collecting for the study all diagnoses included under the headings of "Mood disorders" (except bipolar disorders, i.e., F32 to F39), and "Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders" (F40-F48). This set of diagnoses were grouped under the name of "extended adjustment disorders", since a large part of the patients included presented an adjustment disorder. This category - Reaction to Severe Stress, and Adjustment

Disorders (F43) - differs from others in that it includes disorders identifiable on the basis of not only symptoms and course but also the existence of one or other of two causative influences: an exceptionally stressful life event producing an acute stress reaction, or a significant life change leading to continued unpleasant circumstances that result in an adjustment disorder. The disorders in this section can thus be regarded as maladaptive responses to severe or continued stress, in that they interfere with successful coping mechanisms. Diagnostics include from Acute Stress Reactions (F43.0) to Adjustment Disorders (F43.2), where symptoms last for at least 2 weeks (World Health Organization, 2016). In all cases, diagnoses were made following clinical criteria, without applying formal interviews given the difficulties caused by the pandemic and the need for strict hygiene measures and isolation of patients and professionals. Patients with other psychiatric diagnoses, such as bipolar disorder or psychotic disorders, were excluded from the analysis due to their limited presence in the sample (Diez-Quevedo et al., 2021). In the case of psychiatric disorders during the year prior to admission, they were established by all those registered by family doctors in primary care-based platforms. In the case of psychiatric disorders during admission, they were constituted by all those registered by the doctors in charge of the patients at admission, mainly infectologists, internists and pulmonologists. Given that the diagnoses were made according to the ICD-10 diagnostic categories and not in relation to structured clinical interviews, the objective of our study was not to specifically study each one of the diagnoses, but rather the set of anxiety disorders and affective symptoms in relation to acute inflammatory processes. Most of the patients included have presented adjustment disorders related to the acute stress caused by the disease.

The first determination of blood tests at admission was considered if made at least during the first 72 hours. The determination of serum concentrations of IL-6 was

performed using a chemiluminescence immunoassay (DxI 800, Beckman Coulter) whereas CPR levels were determined by turbimetry (AU 5800, Beckman Coulter).

2.3. Analyses

First, IL-6 and CRP levels in peripheral blood were compared between the group of patients with depressive or extended adjustment disorders and the group of patients without psychiatric symptoms. Second, blood levels were compared among four groups according to previous year history and current presence at admission of a depressive or an extended adjustment disorder: the "No-Disorder Group" included patients without history and without current diagnosis at admission of depressive or extended adjustment disorder; the "Remitted Group" included patients with a positive previous year history but without current diagnosis at admission; the "Persistent Group" included patients with positive previous year history and also current diagnosis at admission; and the "*De Novo* Group" included patients without previous year history but with current diagnosis at admission of depressive or extended adjustment disorder. Third, all comparisons were adjusted for sex, age, body mass index (BMI), current smoking status, and chronic medical disorders.

Bivariate comparisons between groups defined by the presence or absence of depressive or extended adjustment disorder at admission were made using the Pearson's $X^2$ for dependent categorical variables and a one-way analysis of variance (ANOVA) for continuous dependent variables. Comparisons between the four groups defined by previous history and current presence of depressive or extended adjustment disorder were performed using the Pearson's $X^2$ for dependent categorical variables and a one-way ANOVA for continuous dependent variables with a post-hoc Tukey analyses. In case of non-homogeneity of variances, a Welch analysis with Games-Howell post-hoc correction was performed. Finally, comparisons for IL-6 and CRP among the four

groups were adjusted by the variables previously referred, with a Bonferroni post-hoc correction.

Analyses were executed using IBM SPSS Statistics 22.0.0 for Windows (SPSS Inc, Chicago, IL, USA).

## 3. RESULTS

A total of 2,150 COVID-19 adult inpatients were admitted to the hospital during the study period. The characteristics of the total sample are described in a previous article. (Diez-Quevedo et al., 2021) In 262 of the cases a determination of inflammatory biomarkers was not carried out within the first 72 hours of admission, so they were excluded from the analyses. Bipolar and psychotic patients (n=37) were also excluded. Thus, the final sample was composed of 1,851 patients: 1,093 (59.0%) were male, mean age 61.6 years (standard deviation (SD), 16.6). Six hundred and sixty-one (35.7%) patients had a history of depressive or extended adjustment disorders, and 490 (26.5%) had a current disorder during admission. The No-Disorder Group consisted of 1,036 patients (56.0%), the Remitted Group of 325 (17.6%); the Persistent Group of 336 (18.2%); and the *De Novo* Group of 154 (8.3%). Characteristics of total sample and according to the current presence of depression or extended adjustment disorder are showed in Table 1, and according to the four groups' adscription in Table 2.

Regarding serum levels of IL-6 and CRP, both were significantly higher in the group of patients with depressive or extended adjustment disorders at admission (Table 3): mean IL-6 levels were 114.25 pg/mL (SD, 225.44) in depressive or extended adjustment disorder patients vs. 86.41 pg/mL (SD, 202.97) in patients without such disorders (F=5.783; p=.02). CRP figures were 103.94 mg/L (SD, 91.16) vs. 90.14 mg/L (SD, 85.73) respectively (F=8.524; p=.004). When adjusted for age, sex, medical disorders, BMI, and smoking status, differences remained statistically significant: adjusted means for IL-6 were 111.65 pg/mL (standard error (SE), 9.53) vs. 87.35 pg/mL (SE, 5.63) (F=4.703, p=.03); adjusted means for CRP were 102.14 mg/L (SE, 3.93) vs. 90.79 mg/L (SE, 2.32) (F=6.039; p=.01).

Table 4 shows blood tests results by groups according to the current presence and history of a depressive or extended adjustment disorder, as well as adjusted for age, sex, medical disorders, BMI, and smoking status.

## 4. DISCUSSION

In congruence with most previous studies (Osimo et al., 2020), our results show that serum concentrations of IL-6 and CRP are higher in patients with depressive or extended adjustment disorders than in patients without such disorders, even controlling for sex, age, presence of several chronic medical disorders, BMI, and current smoking status. For instance, Köhler et al. published a recent meta-analysis including 82 studies comprising 3,212 participants with major depressive disorder and 2,798 healthy controls showing that depressive patients had an inflammatory response characterized by increased levels of acute phase reactants (e.g., CRP) and pro-inflammatory cytokines (e.g., IL-6) (Köhler et al., 2017). Interestingly, serum levels in the depressive or extended adjustment group in our sample were 30% higher for IL-6 and 20% for CRP, similar to data from most previous studies in several different populations (Dowlati et al., 2010).

Thus, the analysis in our study comparing patients with some affective disorders with non-disordered patients seems to be reduced to replicating these comprehensive data in the literature, although, to our knowledge, being the first study to confirm these findings in a population of COVID-19 patients. But beyond confirming the relationship of depression and stress-related disorders with inflammation biomarkers, our study raises other several important considerations based on 1) the absolute IL-6 and CRP serum concentrations found, which are clearly higher than those of previous studies, not only in the group of patients with depressive or extended adjustment disorders at admission but also in the control group of COVID-19 patients without such disorders, and 2) the comparison among groups based on the presence of persistent or acute depressive or extended adjustment disorders.

First, we found no differences in IL-6 and CRP concentrations between patients with persistent depressive or extended adjustment disorders and patients in the No-Disorder group. We could hypothesize that this leveling of the figures was the consequence of a tendency in the chronicity of affective processes to reduce inflammation until it equaled that of subjects without depressive or anxiety disorders. This first hypothesis could be supported through the activation hypothalamus pituitary adrenal (HPA) axis as one of the main stress responsive systems. In the face of acute stress, HPA axis provides short-term adaptation to threats (increases in blood glucose, blood pressure, heart rate, but also stimulation of the inflammatory response with increases of inflammatory cytokines in blood). However, under chronic stress HPA axis changes can be associated with altered activity and blunted response to the acute stressor (Lam et al., 2019; Miller et al., 2014). If we consider SARS-COV2 a life-threating situation, that generates and added biological and psychological stress, it is not surprising that those individuals with persistent extended adjustment disorders (chronic stress) would show a blunted HPA axis response and therefore lower increases of inflammatory cytokines in comparison with those with acute disorders. In this sense, we could also justify the higher levels of IL-6 and CRP in the group of patients with *De Novo* (acute) disorders.

However, we believe that a more plausible hypothesis is that this leveling is probably a consequence of the acute infectious process, when IL-6 values step up powerfully (Tanaka et al., 2014). IL-6 increases markedly when emergent stress occurs, such as COVID-19 infection, and the subtle but persistent elevations in chronically depressed patients are no longer observed. That is, in all groups of COVID patients represented in our study, what we are seeing is the product of the acute response of IL-6 as a pro-inflammatory cytokine, and not the sustained chronic stress as it occurs in patients

suffering from persistent depression. In any case further studies are needed to elucidate these hypotheses.

Second, we found that patients with *De Novo* depressive or extended adjustment disorders have significantly higher levels of IL-6 and CRP compared to those in the other groups. If we assume that in the case of COVID-19 IL-6 and CPR figures represent an acute anti-inflammatory mechanism and not a proinflammatory chronic condition, how can we explain these findings? The hypothesis that most probably supports them is that this group of patients was more seriously ill and, therefore, they suffer from a greater cascade of cytokines leading to deleterious clinical manifestations or even acute mortality. As Table 1 showed, patients in the *De Novo* group were more severely ill and presenting with statistically significant greater history of chronic medical conditions such as cardiovascular risk factors, heart disease, chronic renal failure, or cerebrovascular disease. Several of these comorbidities have been more frequently observed among patients with severe COVID-19 (Mudatsir et al., 2021; Yang et al., 2021). However, the question remains. Why is the group of subjects with the most severe COVID also the one with the most *De Novo* depressive or extended adjustment disorders? It cannot simply be the psychological reaction to the perception of severity and poor prognosis, although it may also be a factor involved.

Some authors have suggested that inflammation might be associated with some specific dimensions of symptoms beyond categorical diagnoses, mainly symptoms included under the theoretical framework of RDoC (Insel et al., 2010), into the systems of positive and negative valence, such as those related to motivation and motor activity (anhedonia and fatigue), and to sensitivity to threat (anxiety, arousal, and alarm) (Capuron and Castanon, 2017), symptoms which are common to many medical and psychiatric pathologies. On the contrary, more specific and core symptoms of

depression or anxiety would not be related to inflammation. For instance, in the study by Inagaki et al. (Inagaki et al., 2013) in terminally ill cancer patients, only vegetative symptoms, such as fatigue, appetite loss, and insomnia, were associated with IL-6 levels, while depressed mood and suicidal ideation were not. Similarly, Janicki-Deverts et al. (Janicki-Deverts et al., 2007) also studied the relationship between sickness behavior and pro-inflammatory cytokines by assessing the response of a group of healthy adults to an influenza rhinovirus challenge. The results showed that the increase in IL-6 and other cytokines were associated with a reduced positive affect but not an increase in negative affect, thereby suggesting that there were differences between sickness behavior and depression regarding peripheral inflammation.

In our study, most of the patients were severely asthenic, anorexic, and insomniac (i.e., severely inflamed), but maybe not necessarily anxious or depressed (due to logistical reasons, no scale was administered to the patients to measure these symptoms and diagnoses were not validated by a psychiatrist). It is possible that the group of patients with greater COVID severity presented these symptoms with greater frequency being more frequently diagnosed as having depressive or adjustment disorders when they really presented an overlap with a sickness behaviour. Therefore, clinical features included in the systems of positive and negative valence, such as fatigue, asthenia, anhedonia, or anxiety may be representing an overlap between stress-related disorders and sickness-behaviors and, therefore, might also be clinical markers of severe COVID-19 and worse prognosis.

### 4.1. Conclusions

The absolute levels of IL-6 and CRP are higher than those of previous depression studies. This leveling is probably a consequence of the acute infectious process and cytokines stepping up powerfully covering up persistent chronic subtle elevations in

patients with chronic depression. IL-6 and CRP serum levels are significantly higher in the group of patients with *De Novo* depression and extended adjustment disorders compared to patients with persistent disorders or without such disorders, even after adjusting for several confounders. This group of patients might be more seriously ill and, therefore, suffer from a greater cascade of cytokines leading to deleterious clinical manifestations or even acute mortality, while showing an overlap between sickness behavior and stress-related disorders.

Further studies are needed on the relationship between depression-anxiety and inflammation, evaluating not only categorical psychiatric diagnoses but also specific cross-sectional symptoms, and that focus not only on humoral markers of peripheral inflammation but also on central markers and lymphocyte populations (Beurel et al., 2020).

Our study has several limitations. We were not able to make a systematic mental status evaluation of patients due to the healthcare pressure and the protection and isolation needs of patients and professionals; therefore, diagnoses were clinically based, with no assessments of severity. Severity of COVID-19 disease was neither informed. However, outpatients were not included, and all study patients were seriously ill and required hospitalization in a tertiary hospital. Other limitations included the retrospective nature of our analyses.

## DISCLOSURES

The authors have no conflicts of interest to declare.

## ACKNOWLEDGMENTS

None

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**LEGENDS FOR TABLES**

Table 1. Characteristics of the total sample and according to the presence of a depressive or extended adjustment disorder at admission.

Table 2. Characteristics of the sample according to the history and presence at admission of depressive or extended adjustment disorders.

Table 3. Blood tests results performed during the first 72 hours of admission presented by groups according to the presence of a depressive or extended adjustment disorder at admission.

Table 4. Blood tests results performed during the first 72 hours of admission presented by groups according to the current presence and history of a depressive or extended adjustment disorder.

**Table 1. Characteristics of the total sample and according to the presence of a depressive or extended adjustment disorder at admission.**

| | **Total N=1,851** | **Depressive or extended adjustment disorder at admission** | | **Significance** | | |
|---|---|---|---|---|---|---|
| | | **NO N=1,361** | **YES N=490** | **OR** | **95% CI** | **P** |
| **Sex (males), n (%)** | 1093 (59.0) | 843 (61.9) | 250 (51.0) | 0.64 | 0.52 to 0.79 | <.001 |
| **Age (years), mean (SD)** | 61. 6 (16.6) | 60.0 (16.8) | 65.9 (15.1) | ANOVA F = 46.61; p<.001 | | |
| **History of chronic medical conditions during the year prior to admission (any), n (%)** | 1,541 (83.3) | 1,100 (80.8) | 441 (90.0) | 2.14 | 1.54 to 2.95 | <.001 |
| Dyslipidemia, n (%) | 903 (48.8) | 617 (45.3) | 286 (58.4) | 1.69 | 1.37 to 2.08 | <.001 |
| Type 1 or 2 diabetes mellitus, n (%) | 480 (25.9) | 325 (23.9) | 155 (31.6) | 1.48 | 1.18 to 1.85 | .001 |
| Arterial hypertension, n (%) | 779 (42.1) | 528 (38.8) | 251 (51.2) | 1.66 | 1.35 to 2.04 | <.001 |
| Ischemic heart disease, n (%) | 325 (17.6) | 226 (16.6) | 99 (20.2) | 1.27 | 0.98 to 1.65 | .07 |
| Atrial fibrillation, n (%) | 208 (11.2) | 128 (9.4) | 80 (16.3) | 1.88 | 1.39 to 2.54 | <.001 |
| Chronic heart failure, n (%) | 133 (7.2) | 89 (6.5) | 44 (9.0) | 1.41 | 0.97 to 2.06 | .07 |
| Valvular disease, n (%) | 130 (7.0) | 86 (6.3) | 44 (9.0) | 1.46 | 1.00 to 2.14 | .05 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Chronic renal failure, n (%) | 283 (15.3) | 181 (13.3) | 102 (20.8) | 1.71 | 1.31 to 2.24 | <.001 |
| Chronic obstructive pulmonary disease, n (%) | 193 (10.4) | 141 (10.4) | 52 (10.6) | 1.03 | 0.73 to 1.44 | .88 |
| Sleep apnea / hypopnea syndrome, n (%) | 178 (9.6) | 112 (8.2) | 66 (13.5) | 1.74 | 1.26 to 2.40 | .001 |
| Pulmonary embolism / deep vein thrombosis, n (%) | 145 (7.8) | 93 (6.8) | 52 (10.6) | 1.62 | 1.13 to 2.31 | .008 |
| Bronchial asthma, n (%) | 143 (7.7) | 91 (6.7) | 52 (10.6) | 1.66 | 1.16 to 2.37 | .005 |
| Malignancies, including lymphoproliferative, n (%) | 192 (10.4) | 137 (10.1) | 55 (11.2) | 1.13 | 0.81 to 1.57 | .47 |
| Cerebrovascular disease, n (%) | 123 (6.6) | 70 (5.1) | 53 (10.8) | 2.24 | 1.54 to 3.25 | <.001 |
| **Body Mass Index at admission (kg/m$^2$), mean (SD)** | 28.14 (5.62) | 27.92 (5.20) | 28.64 (6.46) | Welch ANOVA F = 2.710; p=.10 | | |
| **Current smoking status, n (%)** | 128 (6.9) | 100 (7.3) | 28 (5.7) | 0.76 | 0.50 to 1.18 | .22 |

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation

Comparisons between groups were made using the Pearson's $X^2$ for categorical variables and a one-way analysis of variance (ANOVA) for continuous variables. In case of non-homogeneity of variances, a Welch analysis was carried out.

**Table 2. Characteristics of the sample according to the history and presence at admission of depressive or extended adjustment disorders.**

| | **No-disorder group N=1,036** | **Remitted group N=325** | **Persistent group N=336** | ***De novo* group N=154** | **Significance** |
|---|---|---|---|---|---|
| **Sex (males), n (%)** | 691 (66.7) | 152 (46.8) | 135 (40.2) | 115 (74.7) | $X^2$=110.369; p<.001 |
| **Age (years), mean (SD)** | 59.6 (17.1) | 61.4 (16.1) | 66.1 (15.3) | 65.5 (14.8) | Welch ANOVA F=17.986; p<.001 |
| **History of chronic medical conditions (any) during the year prior to admission, n (%)** | 822 (79.3) | 278 (85.5) | 303 (90.2) | 138 (89.6) | $X^2$=28.596; p<.001 |
| Dyslipidemia, n (%) | 448 (43.2) | 169 (52.0) | 196 (58.3) | 90 (58.4) | $X^2$=32.087; p<.001 |
| Type 1 or 2 diabetes mellitus, n (%) | 257 (24.8) | 68 (20.9) | 100 (29.8) | 55 (35.7) | $X^2$=15.166; P=.002 |
| Arterial hypertension, n (%) | 375 (36.2) | 153 (47.1) | 172 (51.2) | 79 (51.3) | $X^2$=34.852; p<.001 |
| Ischemic heart disease, n (%) | 173 (16.7) | 53 (16.3) | 64 (19.0) | 35 (22.7) | $X^2$=4.237; P=.24 |
| Atrial fibrillation, n (%) | 91 (8.8) | 37 (11.4) | 50 (14.9) | 30 (19.5) | $X^2$=21.223; p<.001 |
| Chronic heart failure, n (%) | 63 (6.1) | 26 (8.0) | 31 (9.2) | 13 (8.4) | $X^2$=4.681; P=.20 |
| Valvular disease, n (%) | 56 (5.4) | 30 (9.2) | 30 (8.9) | 14 (9.1) | $X^2$=9.454; P=.02 |
| Chronic renal failure, n (%) | 140 (13.5) | 41 (12.6) | 65 (19.3) | 37 (24.0) | $X^2$=17.660; p=.001 |

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|---|---|---|---|---|---|
| Chronic obstructive pulmonary disease, n (%) | 108 (10.4) | 33 (10.2) | 39 (11.6) | 13 (8.4) | $X^2$=1.177; p=.76 |
| Sleep apnea / hypopnea syndrome, n (%) | 83 (8.0) | 29 (8.9) | 47 (14.0) | 19 (12.3) | $X^2$=11.950; P=.008 |
| Pulmonary embolism / deep vein thrombosis, n (%) | 78 (7.5) | 15 (4.6) | 30 (8.9) | 22 (14.3) | $X^2$=14.233; P=.003 |
| Bronchial asthma, n (%) | 58 (5.6) | 33 (10.2) | 44 (13.1) | 8 (5.2) | $X^2$=24.237; p<.001 |
| Malignancies, including lymphoproliferative, n (%) | 112 (10.8) | 25 (7.7) | 41 (12.2) | 14 (9.1) | $X^2$=4.208; P=.24 |
| Cerebrovascular disease, n (%) | 48 (4.6) | 22 (6.8) | 38 (11.3) | 15 (9.7) | $X^2$=20.930; p<.001 |
| **Body Mass Index at admission (kg/m2), mean (SD)** | 27.92 (5.15) | 27.93 (5.40) | 28.79 (6.69) | 28.31 (5.99) | ANOVA F = 1.222; p=.30 |
| **Current smoking status, n (%)** | 78 (7.5) | 22 (6.8) | 18 (5.4) | 10 (6.5) | $X^2$=1.927; P=.59 |

Abbreviations: SD, standard deviation

Patients were categorized into four groups according to the history and the presence at admission of a depressive or an extended adjustment disorder: 1) The "No-Disorder Group" included patients with no history or current diagnosis at admission of depressive or extended adjustment disorder); the "Remitted Group" included patients with positive history but no current diagnosis at admission); "Persistent Group" (patients with positive history and current diagnosis at admission); and *"De Novo* Group" (patients with no history but current diagnosis at admission of depressive or extended adjustment disorder).

Comparisons between groups were made using the Pearson's $X^2$ for categorical variables and a one-way analysis of variance (ANOVA) for continuous variables. In case of non-homogeneity of variances, a Welch analysis was carried out.

**Table 3. Blood tests results performed during the first 72 hours of admission presented by groups according to the presence of a depressive or extended adjustment disorder at admission.**

| | **No disorder N=1,361** | **Depressive or extended adjustment disorder at admission N=490** | **Significance** |
|---|---|---|---|
| **Interleukin-6 (pg/mL), mean (SD)** | 86.41 (202.97) | 114.25 (225.44) | Welch ANOVA F=5.783 p=.02 |
| **Adjusted interleukin-6 (pg/mL), mean (SE)** | 87.35 (5.63) | 111.65 (9.53) | ANOVA F=4.703 p=.03 |
| **C Reactive Protein (mg/L), mean (SD)** | 90.14 (85.73) | 103.94 (91.16) | Welch ANOVA F=8.524 p=.004 |
| **Adjusted C Reactive Protein (mg/L), mean (SE)** | 90.79 (2.32) | 102.14 (3.93) | ANOVA F=6.039 p=.01 |

Abbreviations: SD, standard deviation; SE, standard error

Comparisons between groups were made using a one-way analysis of variance (ANOVA) for continuous variables. In case of non-homogeneity of variances, a Welch analysis was carried out.

**Table 4. Blood tests results performed during the first 72 hours of admission presented by groups according to the current presence and history of a depressive or extended adjustment disorder.**

| | **No-disorder group N=1,036** | **Remitted group N=325** | **Persistent group N=336** | ***De novo* group N=154** | **Significance** |
|---|---|---|---|---|---|
| **Interleukin-6 (pg/mL), mean (SD)** | 91.76 (211.66) | 69.37 (171.57) | 88.63 (169.45) | 170.13 (308.19) | Welch ANOVA F=5.017; p=.002<br>Games-Howell post-hoc correction:<br>DE NOVO vs NO-DISORDER; p=.01<br>DE NOVO vs REMITTED; p=.001<br>DE NOVO vs PERSISITENT; p=.01<br>NO-DISORDER vs REMITTED ; p=.21<br>NO-DISORDER vs PERSISTENT; p=.99<br>REMITTED vs PERSISTENT; p=.47 |
| **Adjusted interleukin-6 (pg/mL), mean (SE)** | 90.89 (6.49) | 76.98 (11.53) | 88.95 (11.52) | 159.21 (16.80) | ANOVA F=5.839; p=.001<br>Bonferroni post-hoc correction:<br>DE NOVO vs NO-DISORDER; p=.001<br>DE NOVO vs REMITTED; p<.001 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | DE NOVO vs PERSISITENT; p=.003 |
| **C Reactive Protein (mg/L), mean (SD)** | 94.38 (89.09) | 76.63 (72.45) | 93.99 (80.86) | 125.66 (107.47) | Welch ANOVA F=10.186; p<.001<br>Games-Howell post-hoc correction:<br>DE NOVO vs NO-DISORDER; p=.004<br>DE NOVO vs REMITTED; p<.001<br>DE NOVO vs PERSISITENT; p=.007<br>NO-DISORDER vs REMITTED ; p=.002<br>NO-DISORDER vs PERSISTENT; p=.99<br>REMITTED vs PERSISTENT; p=.02 |
| **Adjusted C Reactive Protein (mg/L), mean (SE)** | 93.86 (2.68) | 81.51 (4.75) | 94.53 (4.75) | 117.67 (6.92) | Anova F=6.119; p<.001<br>Bonferroni post-hoc correction:<br>DE NOVO vs NO-DISORDER; p=.008<br>DE NOVO vs REMITTED; p<.001<br>DE NOVO vs PERSISITENT; p=.04<br>NO-DISORDER vs REMITTED ; p=.15<br>Remitted vs persistent; p=.30 |

Abbreviations: SD, standard deviation; SE, standard error

Patients were categorized into four groups according to the history and the presence at admission of a depressive or an extended adjustment disorder: 1) The "No-Disorder Group" included patients with no history or current diagnosis at admission of depressive or extended adjustment disorder); the "Remitted Group" included patients with positive history but no current diagnosis at admission); "Persistent Group" (patients with positive history and current diagnosis at admission); and *"De Novo* Group" (patients with no history but current diagnosis at admission of depressive or extended adjustment disorder).

Comparisons between groups were made using a one-way Welch analysis of variance (ANOVA) with a Games-Howell post-hoc correction. Adjusted comparison by confusing variables (sex, age, medical disorders, body mass index and smoking status) used a Bonferroni post-hoc correction.

**HIGHLIGHTS.**

- Inflammation markers are higher in COVID inpatients with affective symptoms and no previous psychiatric history
- Sickness behavior overlaps with stress-related disorders symptomatology
- Cytokine levels equalize in non-depressed and chronically depressed COVID inpatients
- COVID inpatients with affective symptoms may show a worse prognosis

**Declaration of interests**

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: